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Estudo de solventes baseados em líquidos iónicos para a desterpenação

Evaluation of solvents based on ionic liquids for deterpenation

Dissertação apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Engenharia Química, realizada sob a orientação científica do Doutor Pedro Jorge Marques de Carvalho, Investigador Auxiliar do Departamento de Química da Universidade de Aveiro e coorientação da Doutora Mónia Andreia Rodrigues Martins, estagiária de Pós-Doutoramento do Departamento de Química da Universidade de Aveiro.

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Dedico este trabalho à minha mãe.

“She made broken look beautiful and strong look invincible. She walked with the universe on her shoulders and made it look like a pair of wings.”

o júri

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palavras-chave

Óleos essenciais; Terpenos; Líquidos Iónicos; Desterpenação; Equilíbrio líquido-líquido.

resumo

Os óleos essenciais fazem parte das nossas vidas de uma forma muito abrangente, sendo usados diretamente ou após separação nos seus variados constituintes ou frações. Industrias como a farmacêutica e a química necessitam dos componentes puros dos óleos essenciais enquanto que a indústria alimentar usa normalmente a fração solúvel. Desterpenação é o processo de separação da fração rica em monoterpenos da fração rica em compostos oxigenados.

Ao longo dos anos, vários métodos e tecnologias foram desenvolvidos para efetuar a desterpenação dos óleos essenciais. Neste trabalho foi avaliada a eficácia do uso de líquidos iónicos, um grupo de solventes neotéricos com propriedades excelentes e diversas aplicações, na separação de limoneno e linalool, compostos representativos do óleo essencial da casca da laranja. De forma a aumentar a capacidade de extração deste processo, o solvente dietileno glicol éter dimetílico foi usado como co-extrator.

Visto que existem milhares de líquidos iónicos, inicialmente foi feita uma pré-seleção usando uma ferramenta preditiva, o COSMO-RS. Com base nos valores de seletividade foram selecionados alguns líquidos iónicos com potencial para a separação em questão. O mesmo foi feito para selecionar o co-extrator, onde o cálculo foi baseado na miscibilidade com os terpenos.

Várias misturas ternárias constituídas por limoneno, linalool, DEGDME e líquidos iónicos compostos pelos catiões 1-etil-3-metillimidazólio e 1-butil-3-methylimidazólio e os aniões acetato, hidrogenossulfato, metilsulfato e metanossulfonato foram estudadas experimentalmente. A análise das fases foi feita usando espectroscopia por ressonância magnética nuclear (RMN) de forma a elaborar os diagramas ternários. A maior parte dos resultados experimentais estão em concordância com as previsões obtidas usando o COSMO-RS, validando assim esta ferramenta na seleção de líquidos iónicos para a desterpenação. Os resultados mostram que o melhor líquido iónico para esta separação é o 1-butil-3-metilimidazólio hidrogenossulfato.

keywords

Essential Oils; Terpenes; Ionic Liquids; Deterpenation; Liquid-liquid equilibria.

abstract

Essential oils are part of our lives in many different ways, being used directly or after separation into their components or fractions. Pharmaceutical and chemical industries are some examples of industries that use the pure components of essential oils while food industry normally uses the soluble fraction. Deterpenation is the separation process into the fraction rich in monoterpenes and the fraction rich in oxygenated compounds.

Over the years, different methods and technologies were developed and studied to deterpenate essential oils. In this work, the use of ionic liquids as separation agents in the extraction of limonene and linalool, the representatives terpenes of citrus essential oil, was evaluated. To improve the capacity of the extraction, DEGDME was used as a co-extractant.

Since there are millions of possible ionic liquids, initially a pre-selection was done with the use of the predictive tool COSMO-RS. Based on the selectivities, some ionic liquids with potential for the separation were selected for further investigation. The same was done for the co-extractant selection; however the calculations were based on the miscibility with the terpenes.

Several ternary mixtures constituted by limonene, linalool, DEGDME and the ionic liquids composed of the cations 1-ethyl-3-methylimidazolium and 1-butyl-3-methylimidazolium and the anions acetate, hydrogensulfate, methylsulfate and methanesulfonate as anions were studied experimentally. The quantification of the mixtures was performed using nuclear magnetic resonance (NMR) analysis. Most of the results are accordingly to COSMO-RS predictions validating this model for the selection of ionic liquids for the deterpenation process. The results show that 1-butyl-3-methylimidazolium hydrogensulfate is the best ionic liquid for this separation.

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Nomenclature

Abbreviations

Ar, Argon
CO_2, Carbon Dioxide
COSMO-RS, COnductor-like Screening MOdel for Real Solvents
CSM, Continuum Solvation Model
DEG, Diethylene Glycol
DEGDME, Diethylene Glycol Dimethyl Ether
DEGME, Diethylene Glycol Ether
DES, Deep Eutectic Solvents
ES, Eutectic Solvents
GCMs, Group Contribution Methods
ILs, Ionic Liquids
LLE, Liquid Liquid Equilibria
NMR, Nuclear Magnetic Resonance

Ionic Liquid Cations

$[N_{1111}]^+$, Tetramethylammonium
$[C_2mim]^+$, 1-Ethyl-3-methylimidazolium
$[C_4mim]^+$, 1-Butyl-3-methylimidazolium
$[C_1py]^+$, 1-Methylpyridinium
$[C_2\ py]^+$, 1-Ethylpyridinium

Ionic Liquid Anions

$[BF_4]^-$, Tetrafluoroborate
$[CF_3CO_2]^-$, Trifluoroacetate
$[CF_3SO_3]^-$, Triflate
$[CH_3CO_2]^-$, Acetate
$[CH_3PhSO_3]^-$, Tosylate
$[CH_3SO_3]^-$, Methanesulfonate
$[CH_3SO_4]^-$, Methylsulfate
$[Cl]^-$, Chloride
$[C_2H_6O_4S]^-$, Ethylsulfate
$[HSO_4]^-$, Hydrogensulfate
$[N(CN)_2]^-$, Dicyanamide
$[NTf_2]^-$, Bis(trifluoromethylsulfonyl) amide
$[OMs]^-$, Mesylate
$[PF_6]^-$, Hexafluorophosphate
$[SbF_6]^-$, Hexafluoroantimony
$[SCN]^-$, Thiocyanate
$[SO_4(C_2H_4O)_2CH_3]^-$, 2-(2- methoxyethoxy) ethylsulfate)
$[TFA]^-$, Trifluoroacetate
$AlCl_3^-$, Aluminium Chloride

Symbols

k, Capacity
P_c*, Critical Pressure*
S, Selectivity
T_c*, Critical Temperature*
T_b*,* Boiling Point
β*,* Distribution coefficient
γ*,* Activity coefficient
M, Molar Mass

Subscripts & Superscripts

∞, infinite dilution
a, area
i, component i
j, component j
nrH , number of hydrogens
x, molar fraction

1. Introduction

“There is one thing stronger than all the armies in the world, and that is an idea whose time has come.” - Victor Hugo

1.1. General Context

Part of the essential resources of our planet are getting scarce and the excessive exploitation and use are causing environmental damages. Thus, it is important to look for greener and sustainable alternatives in different fields. With this in mind, we can see now that we are returning to the basics, to nature. In order to persist and evolve, novel technologies should thus be investigated to create ways to use what nature offers.

Essential oils are a very important class of natural products. Their first uses can be traced to 10,000 BC by pollen analysis of Stone Age settlements.[1] Being used in medicine, cosmetics and as perfumes, essential oils were and are very important for human life. In the past, their sources were based on plants available in the nearby regions. Nowadays, essential oils are still part of our life, like standalone products and as a raw material or chemical constituents of secondary products, as cleaning products, food preservatives and pharmaceuticals, making their existence and obtention methods of utmost importance. Around the world, the market demanding and production is on a rising trend with 35,000 tons in 2008[1] of essential oils estimated to be produced; among the essential oils the orange essential oil stands out as that with the most significant production slice, with 52,500 tons in 2015.[2] In 2012, Essential Oil Association of India estimated that the global turnover was around 14 billion dollars.[3]

The first research on the constituents of essential oils is attributed to M. J. Dumas in 1833.[1] Using his own method for nitrogen determination,[4] the author showed that essential oils are constituted by oxygen, sulphur, nitrogen atoms and hydrocarbons. Later, the hydrocarbons with the general formula $C_{10}H_{16}$ present in essential oils were named terpenes by Kelule[1], due to their origin in turpentine oil while the constituents with a molecular formula of $C_{10}H_{16}O$ and $C_{10}H_{18}O$ were named camphor although they were still related to terpenes.[1]

Some of the greatest discoveries regarding essential oils and their chemical composition are attributed to O. Wallach.[1] The author realized that "*a great many terpenes formerly designated differently and of supposedly varying constitution are undoubtedly identical*".[5] Moreover, Wallach was the first author to identify pinene, camphene, limonene, dipentene, sylvestrene, terpinolene, terpinene and phellandrene, and to propose the "isoprene rule" for terpenes formed by isoprene units.[1]

After World War II, chromatographic methods emerged allowing to deep characterize the components of essential oils.

Nowadays, terpenes are commonly defined as unsaturated acyclic, monocyclic or polycyclic hydrocarbons[6] that present molecular structures composed by isoprene units (2-methylbuta-1,3-diene).[7] Terpenoids are oxygenated derivatives of terpenes such as alcohols,

aldehydes, ketones, carboxylic acids and ethers. This subclass of terpenes will from now will be referred just as terpenes.

Limonene, linalool and carvacrol are three of the many existing terpenes present in our daily lives, namely on cleaning products, perfumes, air fresheners, food additives, pharmaceuticals. Their main functions are the addition of flavour, fragrances and medicinal properties to the final products. Limonene, $C_{10}H_{16}$, is a clear and colourless cyclic hydrocarbon, liquid at room temperature and with a normal boiling point of T_b = 450.15 K[8] (Figure 1, on the left). This terpene is mostly used as fragrance in cosmetic and cleaning products and as a flavour component in pharmaceuticals and food products.[7,8] Citrus essential oil is one of the richest sources of limonene containing approximately 83% of this compound.[1] Linalool, $C_{10}H_{18}O$, is an acyclic alcohol (Figure 1, on the right) that can be found in Ho leaf essential oil (95% of its composition)[7] and in citrus essential oil (around 9% of its composition)[9]. Since it has a floral scent, linalool usage falls in perfumed hygiene and cleaning products, in insecticides and is an important intermediate in the fabrication of Vitamin E.[10] Linalool, like limonene, is also liquid at room temperature with a normal boiling point of T_b= 471.15 K.[11]

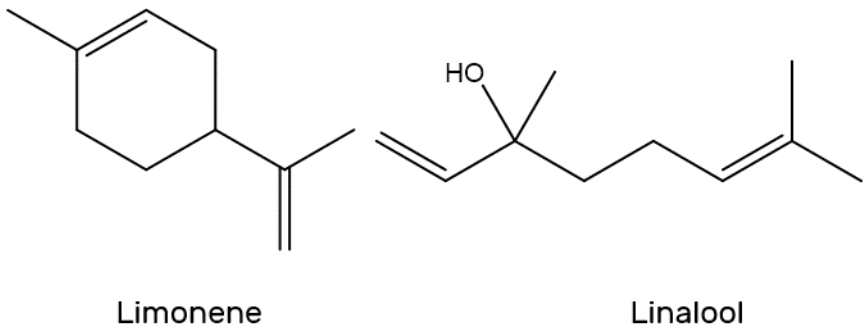


Figure 1. Molecular structure of limonene on the left and linalool on the right.

1.2. Extraction Processes

1.2.1. From the plant to the oil

Many methodologies have been applied for the extraction of essential oils from plants or animals. These fall into four main categories: tapping, expression, distillation and solvent extraction[7]:

- Tapping: Damage of the tree bark and subsequent collection of the resin. It is used, for example, to collect latex for posterior rubber production;

- Expression: Oils are forced out of their natural sources by physical pressure. For example, the squeezing of orange peel will release orange based citrus essential oil;
- Distillation: Isolation of the volatile constituents of the oil by distillation. This process can be divided in 3 different methods:[4]
    - Dry distillation: Uses high temperatures, usually in direct contact with a flame;
    - Steam distillation: Water or steam is used with the oil to limit the temperature of the process in 373.15 K;
    - Hydrodiffusion: The same process as the steam distillation. but the steam is introduced at the top, making the oil cells to diffuse to the steam and collected at the bottom.
- Solvent extraction: The essential oil is extracted with the use of a solvent; it comprises 3 categories:
    - Ethanolic extraction: consists in using an ethanolic solution as solvent, it is mainly used in ambergris;
    - Enfleurage: consist in mixing the raw material with purified fat;
    - Simple solvent extraction.

The processes mentioned above allow obtaining crude essential oils, i.e. a mixture of many components including terpene hydrocarbons and their oxygenated derivatives. Although some essential oils applications do not require further purification or separation processes, as aromatherapy, in some other applications, as in pharmaceutical and chemical industries, it is mandatory to have the essential oils purified or deterpenated or their components isolated.

1.2.2. From the oil to the desired components

Deterpenation is the name given to the separation process the essential oil in two fractions, one rich in oxygenated compounds and other rich in terpene hydrocarbons. This process prevents problems in industrial applications related to the compounds low solubility in water and alcohols and their possible oxidation. The techniques to deterpenate an essential oil or to collect a specific pure terpene from the oil are essentially the same:[13]

- Adsorption Chromatography;
- Vacuum Distillation;
- Solvent Extraction.

Even though adsorption chromatography is one way to separate the essential oil components, in a large-scale it is not feasible. The main problem is to generate a column with

the necessary characteristics to achieve the separation and desired quantities while keeping the costs reduced.[13] Thus, this separation technique will not be explored in this work.

1.2.2.1. Distillation

Most of the components responsible for aroma and flavour have normal boiling points between 423-453 K and 513-553 K and thus, can be removed by fractional distillation under vacuum.[13] However, due to the similar boiling points this technique presents low selectivity, and removes at same time monoterpenes and some of the oxygenated compounds, making the separation difficult if not impossible and leading to final products with low quality and low purity.[14] Moreover, the use of heat may lead to some of the compounds' flavour and aroma degradation.

1.2.2.2. Separation agents

Solvent extraction or liquid-liquid extraction is a separation method based on the compounds' solubility differences and immiscibility. Aiming at an efficient extraction, the solvent or extractant must have: a good distribution coefficient (β>1), *i.e.*, it should dissolve the solute well; and a high selectively, meaning it should preferentially dissolve the target compound over the others.[13] Besides the capacity to extract the solute from the solution, there are other factors to consider when choosing the solvent, like costs, toxicity, physical properties and recoverability.[13]

In the last years, different solvents, like ethanol[15–18], acetonitrile[19], aqueous solutions of the former solvents, and more recently eutectic and deep eutectic solvents[20–22], ionic liquids[23–28] and supercritical fluids[29–33] have been investigated to extract and separate terpenes from essential oils. All these solvents present advantages and disadvantages as further discussed in the following sections.

Membranes

Membrane separation operates at low temperatures and in the absence of a vapour-liquid interface,[13] with the separation occurring by mass transfer over a physical barrier between the two coexistent phases.[34] Moreover, membrane technology present small space requirements.[13] To separate a mixture where the thermal degradation can be a problem, as it is the case of essential oils, membranes stand as a good alternative. Brose *et al.*[34] investigated the use of a membrane technology to separate the oxygenated and monoterpene rich phases of citrus essential oil by using cyclodextrins (CDs). The process rely on the high selectivity of the CDs to bind with the desired oxygenated compounds, allowing the monoterpenes to fluid through the membrane unit. The authors stated that the

use of the membrane could improve the flow rate control of the organic and aqueous phases, making the process semi-continuous and improving the mass transfer area.[34] However, the efficiency of the membrane was limited to a 6.5% presence of oxygenated compounds[34]. Even though membranes require a small space, have low energy requirements and operational costs, they clog easily and their maintenance costs are high.[13]

Conventional Solvents

Conventional solvents like ethanol and methanol were being used for a long time in different industries and are still investigated by many. Arce *et al.*[35,36] *studied* the behaviour of the ternary mixture of limonene, linalool and ethanol[35] and the quaternary mixture of limonene, linalool, ethanol and water.[36] The systems tie-lines have opposite slopes and a selectivity higher than 1, meaning that the separation using the solvent aqueous solutions is plausible.[13] In 2008, Gramajo de Doz *et al.*[37] studied the ternary system limonene, linalool and water contradicting the first paper of Arce *et al.*[35] and claiming that the mentioned ternary system has a narrow solubility region in the studied temperatures. In 2015, Gonçalves *et al.*[17] studied the same system and showed that the presence of water in the system changes the extraction efficiency by lowering the solubility and increasing the selectivity between oxygenated compounds and terpenes hydrocarbons.

Processes involving conventional solvents often include a distillation unit which may induce thermal degradation on the desired product.[13] Thus, researchers are dedicating their time studying and developing new technologies and different solvents to deterpenate essential oils and thus, separate its constituents without the need of a distillation as a final separation process to avoid degradation.

Supercritical Fluids

Carbon dioxide (CO_2) is one of the most studied supercritical fluids in industry due to its approachable critical parameters (T_c=304.1 K; P_c=7.38 MPa)[31], low cost, non-flammability and non-toxicity.[31] The critical properties of CO_2 allow the use of low temperature processes avoiding thermal degradation of essential oils, but also an easy separation of the oil from the CO_2 just by reducing the pressure.[31]

The separation of monoterpenes from oxygenated compounds with supercritical fluids was evaluated by many authors.[29,31–33] Sato *et al.*[32] evaluated the impact of supercritical carbon dioxide on the separation of limonene, linalool and citral. The authors have shown that a temperature gradient improves the extraction due to the differences in the solubility. A slightly increase of the pressure enhanced the mass transfer rates of the process. The authors concluded that the process should operate between 313 to 333 K and at 8.8 MPa.[32] However, when the pressure was increased, even though the yield increased as well,

the selectivity decreased, due to an incompatibility between high selectivity and high solubility. Vieira de Melo *et al.*[33] investigated the limonene and linalool system reporting that the extraction is possible using a high flow of supercritical fluid, however, when the limonene/linalool mass ratio increases, the degree of difficulty of the separation increases as well.

Eutectic and Deep Eutectic Solvents

Eutectic Solvents (ES) and their subgroup Deep Eutectic Solvents (DES) are mixtures of two or more compounds bonded by hydrogen bonds to form a eutectic mixture that is characterized by a melting point lower than that of its starting components.[38] Usually, in DES a quaternary ammonium salt acts as hydrogen bond acceptor and the hydrogen bond donor is an anion chosen to be suitable to the extraction. The interactions between these molecules develops a charge delocalization through hydrogen bonding, causing the decrease of the melting point in the mixture.[39] These neoteric solvents are consider by many as an emerging class of green solvents due to their interesting properties like low toxicity, non-flammability, non-volatility and biodegradability – depending on the starting materials used.[40]

Ozturk *et al.*[21] studied DES as an extractant in the deterpenation process of citrus essential oil. A DES based on glycerol and choline chloride, in wide concentration range, with and without water was evaluated as solvent to separate limonene from linalool. The authors concluded that the deterpenation of citrus essential oil was possible, with the highest extraction capacity reached for the "pure" DES. In mixtures involving water there was a decrease in the distribution coefficients and an increase in the selectivity, due to the increased polarity of the solvent.[21]

Great attention has been given to DES to substitute organic solvents and other emerging solvents in extraction processes. However, their industrial application is limited by the knowledge of their physico-chemical properties, possible toxicity and corrositivity.[38]

Ionic Liquids

Ionic liquids (ILs) have attracted researcher's attention in the past years, with the number of papers and patents achieving thousands.[41] These solvents are defined as molten salts that are liquid in a large range of temperatures[41] and even though different ILs can have very different properties, some of the more interesting ones are negligible vapour pressure, non-flammability, thermal stability and wide liquid phase range.[42] ILs are usually constituted by a large organic cation and an organic or inorganic anion and the combinations of cation/anion confer the possibility of tuning their properties, giving to ILs the designation of "*designer solvents*".[43] The fact that ionic liquids can be used in chemical reactions and

processes at low temperatures decreases the energy costs and the risks of thermal degradation, meeting the necessity to keep the characteristics of the desired compounds intact and avoiding unnecessary costs.[41]

ILs cations differ mainly depending on the compound family that can be ammonium, sulphonium, phosphonium, imidazolium, pyridinium, thiazolium, pyrazolium, among others and these bases are usually completely substituted[41]. ILs anions can be divided into six main groups based on:

- $AlCl_3$ and organic salts;[44]
- anions like $[PF_6]^-$ [45,46], $[BF4]^-$[47,48], and $[SbF_6]$[46];
- amides[49–52];
- alkylsulphates[53], alkylsulphonates[54], alkylphosphates[55], alkylphosphinates[55] and alkylphosphonates;
- mesylate[56,57]($CH_3SO_3^-$), tosylate ($[CH_3PhSO_3]^-$)[57], trifluoroacetate ($[CF_3CO_2]^-$)[58], acetate ($[CH_3CO_2]^-$)[52], thiocyanate $[SCN]^-$) [59], triflate ($[CF_3SO_3]^-$) [46,56,60]and dicyanamide ($[N(CN)_2]^-$)[61,62];
- borates[63] and carborates.

ILs have been applied to the separation and extraction of essential oils. In 2007 Arce *et al*.[24] studied the limonene and linalool binary system using as extractant the ionic liquid 1-ethyl-3-methylimidazolium ethylsulfate, $[C_2mim][C_2H_6O_4S]$, at 298.15 K and 318.15 K.[24] The authors reported a low value of solubility for limonene in the IL at 298.15 K and 318.15 K and a large heterogeneous region with low temperature dependency. Nonetheless, the tie-lines slope present a high temperature dependency. The authors concluded that the solute distribution and respective selectivity are acceptable. However, a quick review of the mentioned system with 1-ethyl-3-methylimidazolium methanesulfonate, $[C_2mim][CH_3SO_3]$, reveals that from a thermodynamic point of view this system would be more interesting since the solute distribution and selectivity were higher than for the studied IL ($[C_2mim][C_2H_6O_4S]$).[24]

Later, Francisco *et al.*[25] investigated the capacity of 1-ethyl-3-methylimidazolium 2-(2-methoxyethoxy) ethylsulfate ($[C_2mim][SO_4(C_2H_4O)_2CH_3]$) to extract the citrus essential oil components. The authors conducted the study at three different temperatures (298.15, 308.15 and 318.15) K and reported a large immiscibility region and small temperature impact on the LLE. The extraction shows high selectivity but the low solute distribution ratio indicates that a large quantity of solvent is needed.[50]

Lago *et al*.[26–28] studied the deterpenation of citrus essential oil with different ILs, comprising imidazolium- and pyridinium-based cations with sulfate-, methylsulfate-, ethylsulfate- and acetate-based anions.[26] They compared these ILs with others already published in literature and claimed that a remarkable effect is observed when shifting the

cation alkyl substituent chain from methyl to ethyl. Nonetheless, both systems have low solute distribution ratios which restrains their usage at an industrial scale. Furthermore, the authors concluded that ILs presenting imidazolium-based cations have slightly better results than the pyridinium ones. Also in 2011, Lago *et al.*[27] studied the deterpenation of the citrus essential oil with the use of three 1-alkyl-3-imidazolium bis(trifluoromethylsulfonyl) amide ([$C_n$mim][NTf_2], with *n=2, 6 and 10)* ionic liquids, and compared the effect of the variation of the cation alkyl chain length on the terpenes extraction.[27] The increase of the cation chain length increases the solute distribution ratio but decreases the selectivity. Results from the solute distribution ratio were lower than those reported for [C_2mim][CH_3SO_3] and [C_2mim] [$C_2H_6O_4S$].[27]

Finally, Lago *et al.*[28] studied the extraction behaviour of 1-ethyl-3-methylimidazolium acetate ([C_2mim][CH_3CO_2]) and 1-butyl-3-methylimidazolium acetate ([C_4mim][CH_3CO_2])[28] showing that these ILs present better results than any other reported up to then, especially at low linalool concentrations (at the beginning of the deterpenation). Authors related the results obtained with a preferential interactions between the acetate anion and the hydroxyl group of linalool.[28] Ionic Liquids have shown promising results as extractants in deterpenation processes, amongst other areas. However, due to the number of existing possibilities there is still a lot of possible combinations and variables unstudied. Thus, in this work ILs are going to be investigated as solvents for the deterpenation process.

It is important to mention that terpenes and terpenoids can be also synthesized, overcoming the extraction and purity limitations found for some natural terpenes and terpenoids, especially when the extraction it is not feasible due to the small amount of component desired in the essential oil. The most common starting components for terpene synthesis are α-pinene and β-pinene, the two major constituents of turpentine, the largest essential oil produced. The decision between synthesis and extraction mainly depends on the cost of the process and the goal for the end product.

1.3. Predictive tool for Ionic Liquids Selection

The fact that we can vary the cation and the anion in the ionic liquid structure and also their substituent chains to adjust the ILs characteristics and properties to the process, makes the number of possible combinations to 10^6 pure ILs, 10^{12} binary mixtures of ILs, 10^{18} ternary mixtures of ILs and so on.[41] Since it is not humanly possible to test every single

combination of ILs, it is essential to have a tool to screen the viability and to narrow to a feasible number the ILs with the highest potential.

COSMO-RS (Conductor-like Screening Model for Real Solvents) is a predictive tool based on a quantum chemical approach, proposed by Klamt and Eckert, that calculates the chemical potential differences.[67] It can be used to predict a large amount of thermophysical properties such a solubilities, activities and/or vapour pressures.[69] The software theory is based on the interaction between the molecular surface charges and merges an "*electrostatic theory of locally interacting molecular surface descriptors*" with "*a statistical thermodynamics methodology".*[69]

In the last years, COSMO-RS gained some popularity against other Group Contribution Models (GCMs), since it requires only the molecular structure of the components involved and provides interesting results. Also, the fact that it is an *a priori* predictive method and its general applicability to the entire organic chemistry, due to the few element-specific parameters gives it an advantage.[66]

In 2000, Klamt *et al*.[66] investigated COSMO-RS method to explore its facilities and to compare it to GCMs like UNIFAC. An advantage of GCMs appears to be their extreme speed and low computational requirements, when all group parameters are available, the calculation takes only milliseconds on a computer, however if the group parameters are not available, the calculations can not be done. On the contrary, COSMO-RS requires time-consuming quantum chemical calculations for each compound under consideration, but as soon as these are available, e.g. from a database, COSMO-RS becomes as fast as UNIFAC.[66]

Ozturk *et al.*[21] and Martins *et al*.[70] evaluated COSMO-RS as a predictive tool for the selection of solvents to separate terpenes and terpenoids.

Ozturk *et al.*[21] used COSMO-RS as a tool to predict the performance of DES in the deterpenation of citrus essential oil. The authors calculated the distribution coefficients and selectivity and found that COSMO-RS underestimates the values of both properties but was able to qualitatively reproduce the data trends[21]. Martins *et al.*[70], used the same predictive tool to calculate the activity coefficients at infinite dilution of terpenes in ILs, at different temperatures. COSMO-RS was found to be a useful tool for the screening of ionic liquids and identify those with the highest potential for terpenes and terpenoids extraction. The authors[23] showed that, in order to achieve the maximum separation efficiency, polar anions should be used combined with non-polar cations.

Most of the studies involving COSMO-RS and ILs (and DES) claim that this predictive tool can be used as a qualitative predictive tool, however underestimates some properties. This can happen due to the fact that ionic liquids are a neoteric group of solvents and the knowledge we have on their properties is still not enough and especially in COSMO-RS, there is

not a database for these compounds yet. Anyway, COSMO-RS stands as a great starting point if one aims at screening a large group of solvents for a target application and it will be the prediction tool used in this work.

1.4. Scope and objectives

With so many ionic liquids and with their magnitude of applications in several fields, these solvents are undoubtedly an important research topic. However, due to the number of possibilities and their intrinsic complexity, there are a lot of knowledge to be gathered. This thesis aims to contribute to expand the knowledge on ILs as extractants for the deterpenation process of citrus essential oil and of COSMO-RS as a predictive tool. Moreover, since the selectivities presented in literature studies are low, in this thesis, the effect of a co-extractant in the selectivity of the separation of the oil is going to be evaluated.

Citrus essential oil was chosen as the model oil due to its availability and applicability. It will here be represented based on limonene and linalool, its main representatives, like in many other studies found in literature.[13,21,26–28,32,34]

Due to the number of possibilities of ILs that can be used in a separation process like this one, is necessary to narrow it to a feasible number of options to be studied. In Chapter 2: Extractant & Co-extractant Selection a brief introduction to the theory behind COSMO-RS model is given. Moreover the procedure to use COSMO-RS and to screen the ionic liquids and the co-solvents for the deterpenation of citrus essential oil is addressed. Results are presented in Section 2.3.

To evaluate the results of COSMO-RS predictions and to study the possible extractant and co-extractant for this deterpenation it was necessary to do some experimental measurements. ^{1}H NMR analysis was used as a quantitative technique. In Chapter 3 Experimental Procedures & Methodology, a detailed explanation of the methodology and a description of the materials and equipments used in this work are presented, including the methodology to prepare the mixtures used and the analysis of the ^{1}H NMR spectra.

Experimental results can be found in Support Information. These allow the quantification of the samples and the construction of diagrams to compare with the data predicted by COSMO-RS, and consequently allow the selection of the ionic liquid and solvent for the deterpenation of the citrus essential oil. These results can be found in Chapter 4 Experimental Results.

Finally, in Chapter 5 the work conclusions are stated and a reference to future work is provided.

2. Extractant & Co-extractant Selection

“In any given moment, we have two options: to step forward into growth or to step into safety.” - Abraham Maslow

2.1. Theory

COSMO-RS (Conductor-like Screening Model for Real Solvents) was developed by Klamt and Eckert[71] and combines an electrostatic theory of molecular surface interactions and a statistical thermodynamics. COSMO-RS model is able to predict a great number of thermodynamic properties such as vapour pressures, solubilities and activity coefficients, making it a relevant tool in chemical engineering problem solving.[65,66] Some of the concepts related with the COSMO-RS theory are not present in this work, but can be found elsewhere.[64,66]

In GCMs based on local composition, like UNIFAC (semi-empiric approach for predicting the activity coefficients using the interactions of its functional groups), the interactions between molecules are considered as nearest neighbour interactions of pairwise approaching molecular surfaces, however in COSMO-RS only the interactions of the condensed phase are treated the same. Instead of being described as pairwise group parameters, they are calculated as an expression of the local surface descriptors such as local screening charge density. This density is calculated as if the molecule would be enclosed in a virtual conductor and can be calculated using quantum chemical programs with a continuum solvation model (CSM).[66]

Designed for isolated molecules, quantum chemical methods were improved to combine a molecule quantum chemical description with a close continuum characterization to achieve a state where they could meet industry's expectations in representing a rigorous image of the molecular surroundings in solution.[66] For a given molecular geometry, COSMO creates a molecular cavity and describes that cavity in small segments, with a certain density that ends in a screening charge and it is able to convert that into the electrostatic potential of the solute in those created segments.[66]

Even though there has been a successful application of CSMs for some properties, like in partition coefficients, CSMs by themselves can not be used to describe the activity of molecules in solvents because they lack statistical thermodynamics. COSMO-RS model, using the basis of CSMs but with the molecules embedded in a virtual conductor, opens the possibility to calculate thermodynamic properties for mixtures making it close to the real situation, especially in polar solvents.[66]

COSMO-RS enables the prediction for any system that has no group parameters available to use GCMs. Also, COSMO recognises the differences between different groups of substituents in a molecule, since they all contribute differently in their quantum chemical calculations, something that is not possible when using a GCM. [66]

In this work, COSMOTherm® software, an interface that provides an efficient implementation of the COSMO-RS method, is used to predict the capacity (solubility at infinite dilution) and selectivity of ILs for a terpene separation by evaluating the activity coefficients at infinite dilution and the excess enthalpy.[72] This software is based on the COSMO-RS theory and allows the prediction of many properties just by introducing a COSMO file for each pure compound in the mixture in study. This COSMO files (.cosmo) need to have the molecules or ions in their minimum energy state, to achieve optimal results. This optimization involve several steps as described in Figure 2.

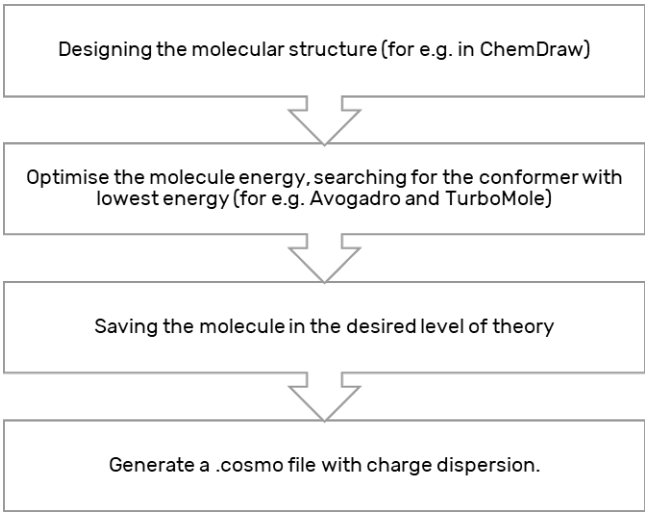


Figure 2. Scheme of the design of the molecular structure.

In this work, Avogadro was used as the main tool to optimise the molecular geometry of all the molecules used as components for the COSMO-RS calculations. The process used consisted on designing the molecule on ChemDraw and then search for its conformers in Avogadro[73]. The optimal geometry configuration was obtained with the conformer with the lower state of energy. TurboMole[74] is then used to perform the calculations of electronic density and molecular geometry and finally, to save the optimised molecule in a COSMO format. In this work, the energy level used was TZVP.

The method for the calculation in COSMOTherm process is simple and it comprises the following steps:

1. Choice of the needed compounds;
2. Choice of the desired property ;
3. Choice of the specific parameters, like composition, temperature, pressure, etc.

In this work, three different types of calculations were performed using COSMOTherm: Ionic Liquids Screening, Phase Diagrams of Liquid-Liquid Equilibria (LLE) and Partitioning Liquid Extraction. A more detailed description of each method is given in the next section *Ionic Liquid Selection.*

2.2. Procedure

2.2.1. Ionic Liquid Selection

As stated in the *"General Context"* section, the number of cations and anions combinations feasible to be used for the synthesis of an IL can reach 10^{12}. Thus, the use of COSMO-RS, as a prediction tool is extremely relevant and necessary to identify those with the highest potential for the intended separation.

To select the ionic liquids with potential for the separation proposed in this work, COSMOTherm was used to calculate the capacity, which corresponds approximately to the molar fraction of the solute in the IL phase, and the selectivity towards limonene and linalool. These calculations were done by using the activity coefficients at infinite dilution, predicted using COSMO-RS. The terpenes molecules were inserted as pure compounds in the software, while the ionic liquids were introduced separately as anions and cations. Selectivity, *S*, and capacity, *k*, were defined by equations 1 and 2, respectively:

$$S_{ij}^{\infty} = \gamma_i^{\infty} / \gamma_j^{\infty} \quad (1)$$

$$k_j^{\infty} = 1/\gamma_j \quad (2)$$

where the subscript *i* corresponds to limonene and *j* to linalool.

In this work, part of the COSMO-RS files used in the screening were taken from a database created by PATh[75] investigation group. This database includes a vast number of ILs cations and anions optimized files, allowing to do many different combinations. This database was successfully used in diverse works and various fields[23,70], being frequently updated. In addition to the list available, a few important COSMO-RS files were optimized in this work to compare with some ILs available in the laboratory, namely:

- (1-Hexyl)trimethylammonium;
- (1-Tetradecyl)trimethylammonium;
- (2-Cloroethyl)trimethylammonium;
- 1-Dodecyltrimethylammonium;
- 1-Isobuty-1-methylpyridinium;
- 3-Methyl-1-propylpyridinium;
- Benzyltributylammonium.

2.2.2. Solvent Selection

As stated in the General Context there are several studies where ILs are used directly as the extraction solvent for the process[25,28,36], however, till this moment, there is no other study

where a third component is introduced in the system to improve the effectiveness of the deterpenation when using Ionic Liquids. However, many authors[15,76,77] studied the introduction of water in the separation of limonene/linalool with conventional solvents and concluded that the selectivity of the separation increased, helping the extraction.

In order to improve the selectivity of the deterpenation, in this work a third component was used as a co-extractant. The next step was to find a solvent to create a second phase in the mixture, creating a ternary system to be studied where one of the terpenes has more affinity to the IL and the other one to the co-solvent added.

The selection of the solvent was made using COSMO-RS to predict the liquid-liquid equilibria. This process consists in two different steps:

1. Prediction of the liquid-liquid equilibria of the solvent and both terpenes;
2. Prediction of the liquid-liquid equilibria of the solvent, the ionic liquid and one terpene.

Both steps were done using the Phase Diagram: Liquid-liquid option of COSMOTherm. A isothermal ternary diagram at 293.15 K was defined.

The solvents studied in this project had already been used in some extractions found in literature,[25,64] however, they were never studied as a co-extractant in combination with ILs:

- Cyclohexane
- Diethylene Glycol (DEG)
- Diethylene Glycol Dimethyl Ether (DEGDME)
- Diethylene Glycol Methyl Ether (DEGME)
- Ethanol
- Ethylene Glycol (EG)
- Ethylene Glycol Ethyl Ether (EGEE)
- Hexane
- MethylCiclohexane
- Pentane
- Tetra Ethylene Glycol (TeEG)
- Tetraethylene Glycol Dimethyl Ether (TeEGDME)
- Triethylene Glycol (TEG)
- Triethylene glycol Dimethyl Ether (TEGDME)
- Water

The results of the prediction of the LLE for the solvent with the terpenes were evaluated and then the second prediction using COSMO-RS was done to select the best solvent option to use in this work.

The option of Liquid-Liquid Equilibria in COSMOTherm, calculates the tie-lines in different pressures while keeping the temperature constant. To assure that the pressure variation had no impact on the behaviour of the tie-lines predicted by this option in COSMOTherm, a second study was conducted using Partitioning Liquid Liquid extraction. This option in COSMOTherm, allows the prediction of the results from a liquid extraction at a

certain temperature and pressure just by introducing the composition of the mixture, delivering as results the composition of both phases that we would obtain if we extracted them.

2.3. Results

2.3.1. Ionic Liquid Selection

COSMOTherm screening was performed with 278 anions and 661 cations resulting in around 11,000 ILs and the results can be found Figure 3, in a contour graphic, with the numerical results reported in Support Information. These results allow the selection of the family or families of ILs with the highest potential for the mentioned separation (limonene/linalool). It is possible to observe (Figure 3) that within the ILs evaluated, only a few based on ammonium, pyridinium and imidazolium cations and carboxylate anion present a selectivity that stands out (S > 120). It is also possible to observe that according to COSMO-RS predictions the most promising ionic liquids to use in this separation are the ones containing ammonium or guanidinium cations (selectivity higher than 145) in combination with carboxylate anions.

Due to time restrictions and the compounds availability in the laboratory, the selection of ILs was a compromise between the families with better selectivity and the ILs available. Based on Figure 3, a first criteria was defined: selectivities higher than 60 (Figure 4). This seems to be a reasonable value to achieve a good separation that is in agreement with other works found in literature.[24]

With the criteria for selecting the ILs for further study set on a selectivity higher than 60, 8 ILs were chosen, combinations of 1-ethyl-3-methylimidazolium ($[C_2mim]^+$) and 1-butyl-3-methylimidazolium ($[C_4mim]^+$) and the anions acetate ($[CH_3CO_2]$), methanesulfonate ($[CH_3SO_3]^-$), methylsulfate ($[CH_3SO_4]^-$) and hydrogensulfate ($[HSO_4]^-$). A total of 10647 ionic liquids were studied. In literature[25], it is possible to find some studies on the capacity of $[C_2mim][CH_3CO_2]$ and $[C_4mim][CH_3CO_2]$ where these ILs showed great performance.

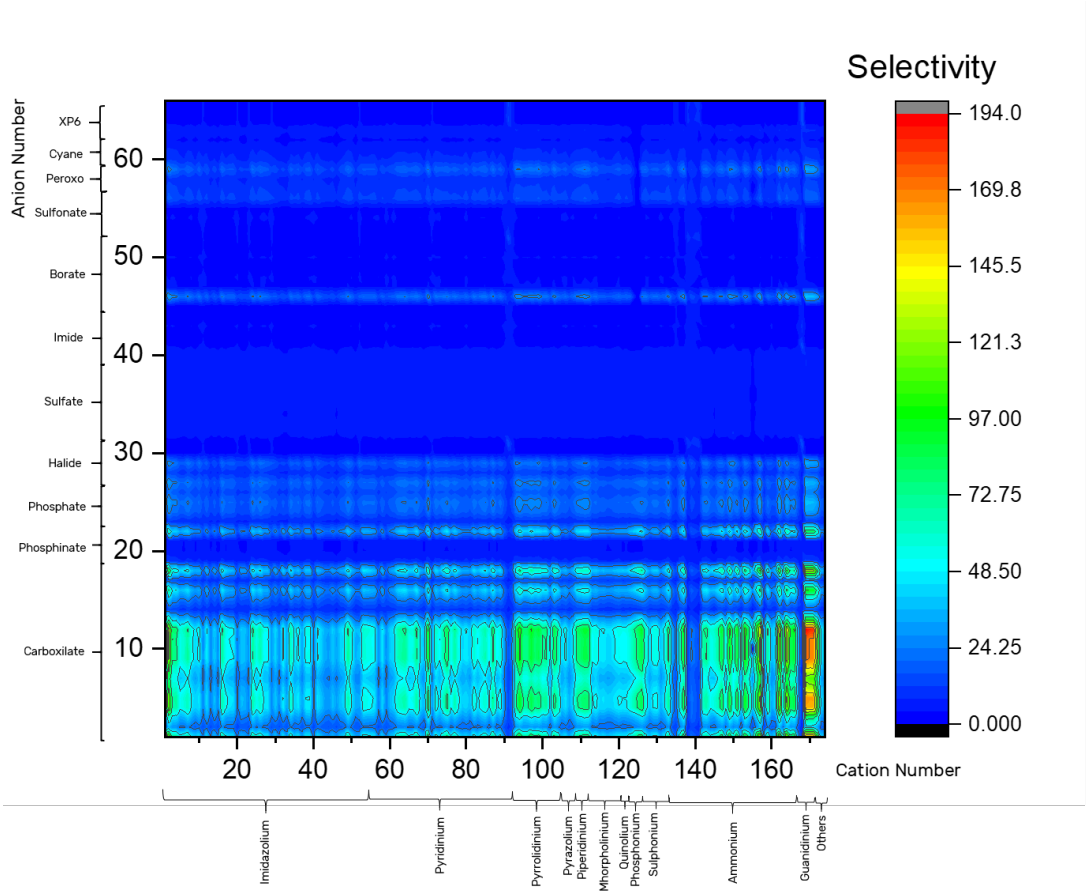


Figure 3. Selectivity for limonene and linalool at 298.15 K in 10486 ionic liquids computed using COSMO-RS. Cations and anions are represented by number and family in the X-axis and Y-axis, respectively.

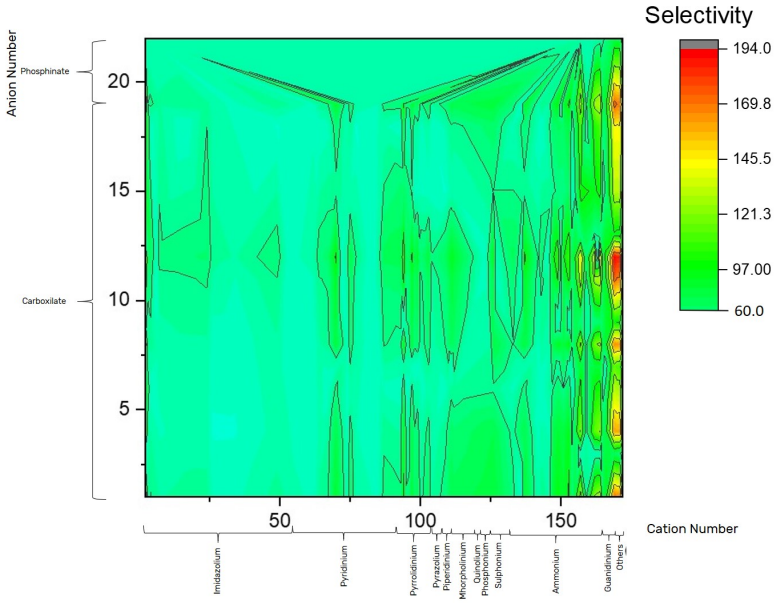


Figure 4. Selectivities higher than 60 for limonene/linalool at 298.15 K in ionic liquids computed using COSMO-RS.

2.3.2. Solvent Selection

The selection of the co-solvent for the extraction in question was done based on the predictions of COSMO-RS regarding the Liquid Liquid Equilibria of terpene:terpene:solvent (step1) and terpene:IL:solvent (step 2).

In Table 1 are summarized the results for all the solvents tested in step 1 while in Figure 5 are displayed the ternary diagrams obtained with the COSMO-RS predictions at 298.15 K (immiscible). It is important to state that the solvents present in Table 1 classified as miscible were completely miscible, not presenting any immiscibility region (no predicted tie-lines with COSMO-RS reporting empty phase diagrams).

Table 1. COSMO-RS prediction results for the solvent selection (step 1).

Solvent	**Miscibility**
Ciclohexane	Miscible
DEG	Figure 5.b)
DEGDME	Miscible
DEGME	Figure 5.c)
Ethanol	Miscible
EG	Figure 5.a)
EGEE	Miscible
Hexane	Miscible
MethylCyclohexane	Miscible
Pentane	Miscible
TeEG	Miscible
TeEGDME	Miscible
TEG	Figure 5.e)
TEGDME	Miscible
Water	Figure 5.d)

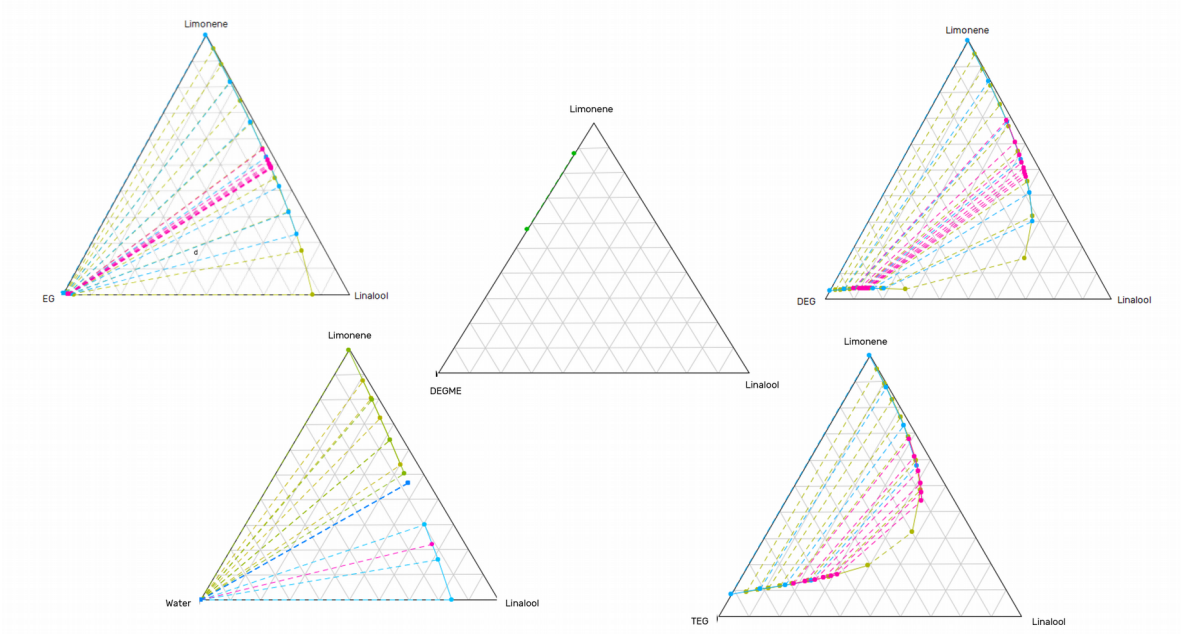


Figure 5. Ternary diagrams predicted at 293.15 K by COSMO-RS of the solvents who presented tie-lines: a) EG; b) DEG; c) DEGME; d) Water; e) TEG.

The miscibility was an important factor to select the solvent to mix with the terpenes, since the goal is to create a mixture where terpenes are both soluble. However, when the ionic liquid is inserted in the mixture an immiscible region should be created allowing the separation of the terpenes while assuring that no cross contamination (IL on the co-solvent phase) takes place avoiding thus, additional separation units. Thus, after discarding the solvents that presented immiscible regions with limonene and linalool, it was necessary to evaluate their behaviour when the ionic liquid is present in the system (step 2). This was made using the same Liquid-Liquid equilibria option in COSMO-RS, where the components of the ternary system were the IL, the terpene and the solvent. The goal was to evaluate the capacity of the solvent and the IL to separate the terpenes in question. The criteria in this step was that the quaternary mixture divided in two ternary diagrams (IL-solvent-limonene & IL-solvent-linalool) should present tie-lines with opposite slopes, which indicates a plausible separation.

In Figure 6 it is possible to observe two examples of ternary diagrams computed in this stage involving DEGDME as a co-solvent, the IL $[C_2mim][CH_3SO_3]$ and the terpenes linalool and limonene. This example shows the differences in miscibility of the mixtures and it is a good example of the desired phase diagram, *i.e.* mixture, since it shows tie-lines with opposite slope denoting a feasible and plausible separation. The results indicate that diethylene glycol dimethyl ether (DEGDME) is the best option for a co-extractant in this separation. This solvent has a low vapour pressure, avoiding additional separation units. The selection of the solvent was done with a comparation of the LLE ternary diagrams for the 8 ionic liquids previously

chosen and all the co-solvents that were not previously discarded. The ternary diagrams predicted by COSMO-RS for this selection can be find in Support Information.

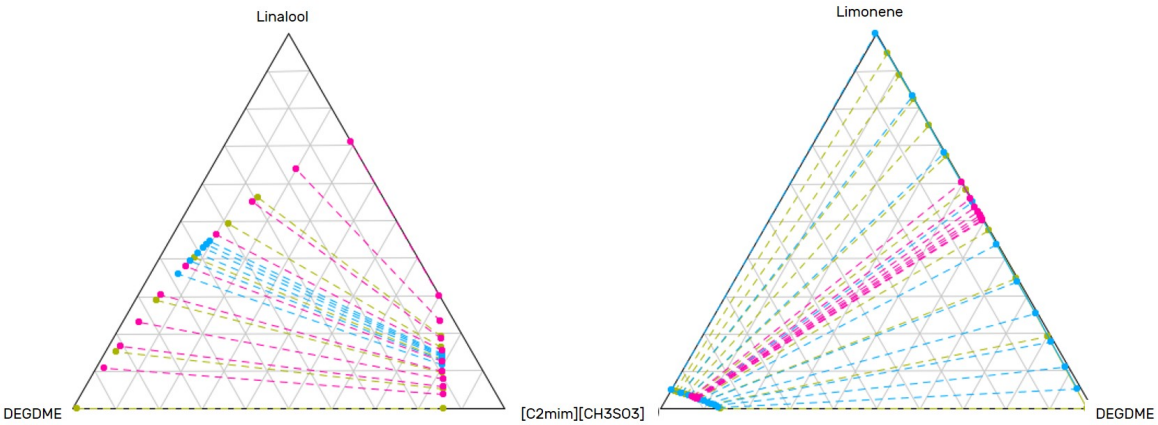


Figure 6. Ternary phase diagram predicted by COSMO-RS for the mixture 1-ethyl-3-methylimidazolium methanesulfonate, linalool and DEGDME, at 298.15 K.

To allow a better analysis of the behaviour of the studied systems and in order to choose some systems to test experimentally, it is helpful to create conjoined ternary phase diagrams that comprise all the combinations in the system. These conjoined ternary phase diagrams are in fact combinations of four ternary diagrams. These representations allow the identification of the mixtures that present one zone of immiscibility in the centre of the conjoined ternary diagram that indicate a plausible extraction, as can be seen in the example presented in Figure 7.

Analysing the conjoined diagram in Figure 7 it is possible to see that the ternary diagram identified with the letter **a** presents no tie-lines, indicating full miscibility in all the composition range. The ternary diagram identified with letter **d** represents the ternary mixture of the solvent, ionic liquid and the terpene limonene. Here, there is a very small region of miscibility between limonene and the solvent, while the rest of the diagram shows immiscibility. The diagram identified with letter **b** represents the same ternary mixture of **d** however the other terpene, linalool. It is easy to verify that the terpene miscibility region with the solvent is bigger than for limonene.

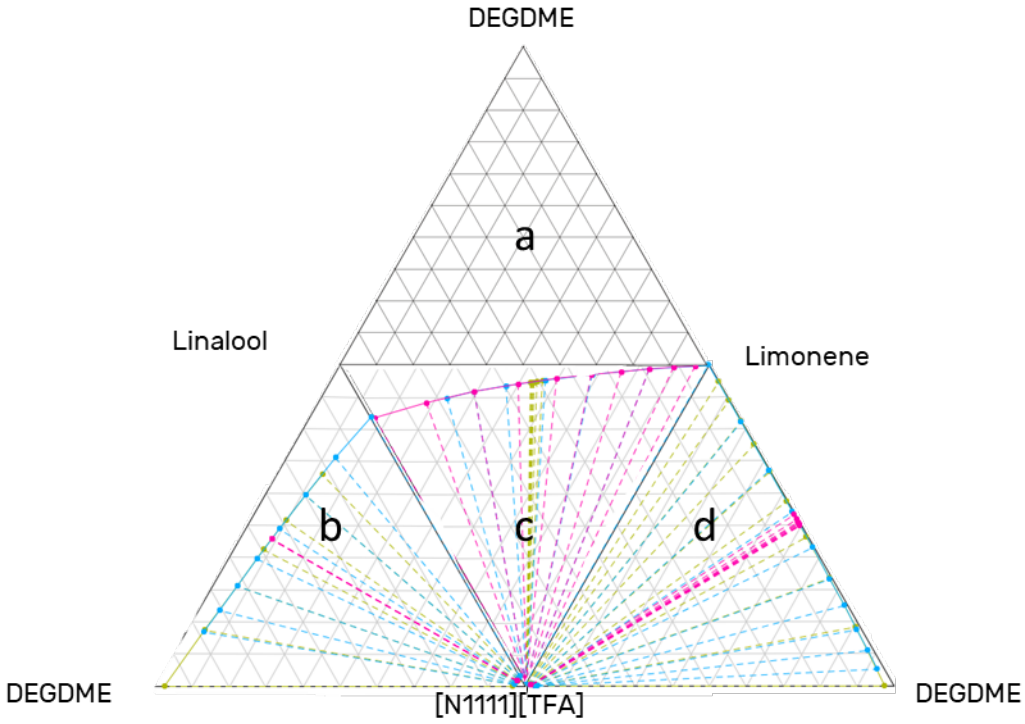


Figure 7. Conjoined ternary diagram for all the possible ternary mixtures in a system containing DEGDME, Tetramethylammonium trifluoroacetate, linalool and limonene, at 298.15 K.

Per last, the diagram identified with letter **c** represents the ternary system between both terpenes and the ionic liquid and as can be seen "it closes the circle", with a small miscibility region for the linalool-IL pair and limonene-linalool pair. The variation of the slope of the tie-lines when going from **b** to **d** indicate a plausible extraction.

The number of possibilities of cations and anions that can be used to create an IL for a simple extraction is enormous, and for a study it is necessary to somehow narrow the possibilities to a few. In this work, COSMO-RS was the model chosen to predict the selectivity of ILs towards the terpenes, limonene and linalool, allowing the choice of 9 ILs to proceed for further investigation. The ILs chosen were $[C_2mim][CH_3CO_2]$, $[C_2mim][HSO_4]$, $[C_2mim][CH_3SO_3]$, $[C_2mim][CH_3SO_4]$, $[C_4mim][CH_3CO_2]$, $[C_4mim][HSO_4]$, $[C_4mim][CH_3SO_3]$ and $[C_4mim][CH_3SO_4]$.

COSMO-RS allowed the prediction of the LLE of ternary mixtures as well, enabling the selection of the co-extractant to use in this work in two different steps. In step 1, the prediction of the LLE of the terpenes and the co-solvent was studied to find a completely miscible mixture and in step 2, the ternary mixtures of IL-solvent-terpene were study to select, based on the predicted results, the mixtures with an opposite slope for each terpene. From the 10 different solvents studied, DEGDME was the one that presented better results.

To confirm the results of COSMO-RS and evaluate its prediction capacity, various ternary mixtures were created in laboratory and analysed using ^1H NMR analysis.

3. Experimental Procedures & Methodology

“In the spirit of science, there really is no such thing as a ‘failed experiment’. Any test that yields valid data, is a valid test.” - Adam Savage

3.1. Materials & Equipments

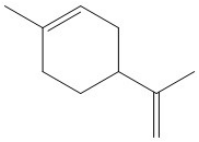
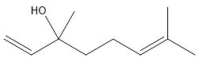
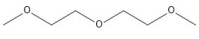
3.1.1. Terpenes & Co-Solvent

The terpenes limonene and linalool were acquired from Aldrich and SAFC and present a mass fraction purity higher than 97% (according with the suppliers). All the terpenes were stored at 278.15 K and were used without further purification.

The solvent diethylene glycol dimethyl ether (DEGDME) was acquired from Sigma with a mass fraction purity greater than 99%. Glymes are known to present high hygroscopicity[78] and thus, 3Å zeolites were placed in contact with the compound aiming to reduce its water content to negligible values. The water content was then measured using a Metrohnn Karl Fischer 831 KF coulometer and was found to be below 300 ppm.

The name, supplier, structure, CAS number, molar mass and purity of the investigated compounds are reported in Table 2.

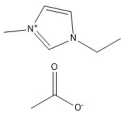
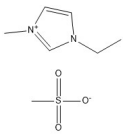
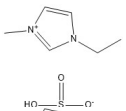
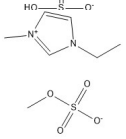
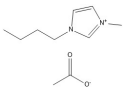
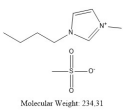
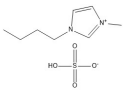
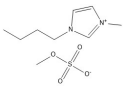
Table 2. Name, structure, Supplier, CAS, molar mass (*M*) and mass fraction purity (declared by supplier) of the investigated compounds.

Compound	Structure	Supplier	CAS	M/g•mol^{-1}	%Mass fraction purity
Limonene		Aldrich	5989-27-5	136.24	97%
Linalool		Aldrich	78-70-6	154.25	97%
Diethylene glycol dimethyl ether (DEGDME)		Sigma	111-46-6	134.18	99.5%

3.1.2. Ionic Liquids

The description of the Ionic Liquids experimentally used in this work is reported in Table 3. These ionic liquids were purified before further use (since the presence of water can compromise their characteristics), under vacuum (0.1 Pa) moderated temperature (298 K) and constant stirring for at least 48h. The water content was then measured using Metrohnn Karl Fischer 831 KF coulometer and was found to be below 300 ppm for all samples.

Table 3. Name, structure, CAS, molar mass (M) and purity (declared by supplier) of the investigated ionic liquids.

Ionic Liquids		Supplier	CAS	M/g•mol^{-1}	%Mass fraction purity
1-Ethyl-3-Methylimidazolium acetate [C_2mim][CH_3CO_2]		Iolitec	143314-17-4	170.21	98%
1-Ethyl-3-Methylimidazolium Methanesulfonate [C_2mim][CH_3SO_3]		Iolitec	145022-45-3	206.26	99%
1-Ethyl-3-Methylimidazolium hydrogensulfate [C_2mim][HSO_4]		Iolitec	342573-75-5	208.23	99%
1-Ethyl-3-Methylimidazolium methylsulfate [C_2mim][CH_3SO_4]		Iolitec	516474-01-4	222.26	99%
1-Butyl-3-Methylimidazolium acetate [C_4mim][CH_3CO_2]		Iolitec	284049-75-8	198.27	98%
1-Butyl-3-Methylimidazolium Methanesulfonate [C_4mim][CH_3SO_3]		Iolitec	342789-81-5	234.31	99%
1-Butyl-3-Methylimidazolium hydrogensulfate [C_4mim][HSO_4]		Iolitec	262297-13-2	236.29	99%
1-Butyl-3-Methylimidazolium methylsulfate [C_4mim][CH_3SO_4]		Iolitec	401788-98-5	250.31	99%

Due to the hygroscopic nature of Ionic Liquids[79] the presence of water in their constitution is highly probable and can be seen as an impurity. To avoid any compromise in the results of this study, the ionic liquids were dried before use and handled in a glovebox with an inert atmosphere. All the ionic liquids and materials needed were inserted in the small antechamber of the M-Braun MB-M0-SE1 Glovebox and the air from the antechamber was evacuated and refilled with Argon for at least five minutes. After removing all the

materials and compounds from the antechamber, the valve was closed and the chamber was left under static vacuum.

All the ionic liquids were weighed into hermetic tubes that allow the posterior insertion of liquids (outside the glovebox) through the lid using a needle. Before leaving the glovebox, all tubes were closed and were not open until the analysis were over to assure that the ionic liquids were dry throughout the whole process.

3.2. Methodology

3.2.1. Ternary mixtures preparation

Ternary mixtures were prepared using a procedure involving several steps aiming to avoid the mixture contamination by water absorption. Glass tubes of 2 mL volume were used to prepare the samples.

First, ILs (previously dried) were weighted at room temperature, inside a M-Braun Glovebox MB-MO-SE1 under an inert atmosphere (Argon) using an analytical balance KERN ALS 220-4N (precision = 2×10^{-4} g). The water content was below 10 ppm during the procedure inside the glovebox.

Then, terpenes and DEGDME were weighted at room temperature with an analytical balance Mettler Toledo XS205 Dual range (precision = 2×10^{-5} g) into the glass tube, using a syringe, that was inserted through the septum, keeping the lid closed to avoid water contamination. In most of the samples, the three compounds (terpene, ionic liquid and DEGDME) formed two phases as soon as they were inserted in the tube. The mixture was agitated in a vortex agitator to promote the phases contact and allowed to equilibrate in an OMRON E5CN equilibrium chamber at 298.15 K (with an uncertainty of 0.05 K) for at least 24 hours. This time is sufficient to assure equilibrium, since literature studies used only 10-12 hours.[24,25,27] Pictures of the samples after being taken out of the equilibrium chamber can be found in Figure 8.

In order to analyse the compositions, samples of both phases were withdrawn using plastic syringes through the septum outlets. Then they were introduced into NMR tubes and analysed in a Bruker Avance III spectrophotometer with ^{1}H resonance of 300 MHz. In Table 4 are presented the different deuterated NMR solvents used to dissolve the samples.

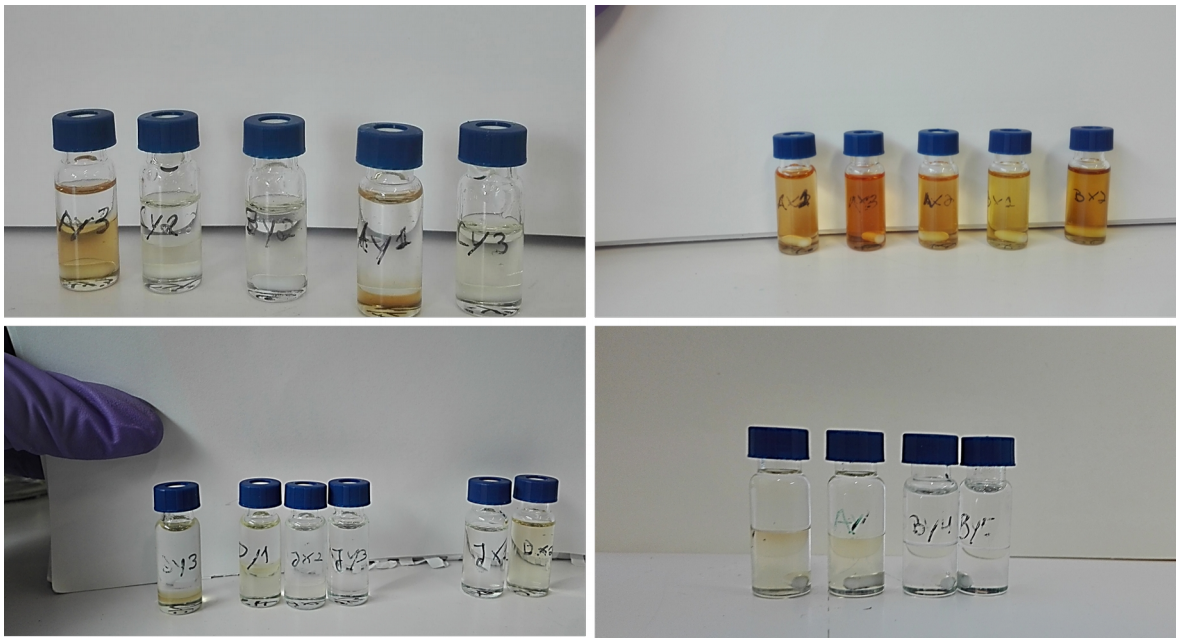


Figure 8. Examples of samples of the ternary mixtures investigated in this work.

3.2.2. ^{1}H NMR Analysis

The analysis of the phases composition and all the pure compounds investigated was carried out by ^{1}H NMR spectroscopy using a Bruker Avance III spectrophotometer with ^{1}H resonance of 300 MHz. This technique was already used in the literature and proved to be adequate for this type of analysis.[24,26–28]

As described above, a drop of each phase was collected with a plastic syringe and inserted into a NMR tube and then mixed with a deuterated NMR solvent (Table 4). After mixing the phase with the solvent, each NMR tube was immediately capped to avoid losses of volatile components and the contamination of water.

It is important to refer, that due to the size of some phases, it was impossible to retrieve a sample without compromising the outcome. This was proved during the NMR analysis, since not only it was expected to obtain tie-lines in different extremes of the diagram, i.e., have 2 phases richer in different components complementing each other, and instead we had two different phases but both with a mixture of the three compounds but mostly because the obtained tie-lines were not coherent showing different and thermodynamically inconsistent slopes as depicted in Figure 10.

As mentioned before, due to the insolubility of some samples in some NMR solvents, different solvents were used. To avoid the solubility problems with the deuterated solvent, capillary tubes could have been used. In this technique, the solvent is inserted in a sealed capillary tube that is inserted into the NMR tubes. The sample is then added but does not has

contact with the solvent. However, this technique requires a bigger sample size and thus could not be used here.

Table 4. NMR solvents used to dissolve the samples of the phases in equilibrium.

Ionic Liquid - terpene	Solvent
$[C_2mim][CH_3CO_2]$ - Limonene	$CDCl_3$
$[C_2mim][CH_3CO_2]$ – Linalool	-
$[C_2mim][CH_3SO_3]$ - Limonene	$CDCl_3$ / DMSO
$[C_2mim][CH_3SO_3]$ – Linalool	DMSO
$[C_2mim][HSO_4]$ - Limonene	$CDCl_3$ / D_2O
$[C_2mim][HSO_4]$ - Linalool	$CDCl_3$ / D_2O
$[C_2mim][CH_3SO_4]$ - Limonene	$CDCl_3$
$[C_2mim][CH_3SO_4]$ - Linalool	$CDCl_3$
$[C_4mim][CH_3CO_2]$ – Limonene	$CDCl_3$ / DMSO
$[C_4mim][CH_3CO_2]$ - Linalool	-
$[C_4mim][CH_3SO_3]$ - Limonene	-
$[C_4mim][CH_3SO_3]$ - Linalool	-
$[C_4mim][HSO_4]$ - Limonene	$CDCl_3$ / DMSO
$[C_4mim][HSO_4]$ - Linalool	D_2O / $CDCl_3$
$[C_4mim][CH_3SO_4]$ - Limonene	$CDCl_3$
$[C_4mim][CH_3SO_4]$ - Linalool	$CDCl_3$ / DMSO

NMR spectra were analysed using MestReNova®. The NMR spectra of the pure compounds are presented in Support Information with the respective peak identification. ChemDraw® predictions and ^1H NMR spectra found in literature were used to help in the peaks identification.

MestReNova® allows to quantify the area below the peaks, providing the possibility to calculate the composition of both phases in equilibrium by proportional quantification of the NMRs of the mixtures using as reference one of the NMRs of the pure compounds. The procedure follows the next steps:

1. Identification of all the peaks corresponding to each hydrogen in the corresponding molecule in the original spectrum;
2. Identification of one isolated peak for each molecule in the mixture spectrum that should be isolated in the original spectrum as well;
3. Calculation of the area below the peaks using integration.

To an easier understanding of the quantification procedure used in this work an example is presented in Figure 9. **A**, **B** and **C** represents the 3 pure compound spectra while D exhibits the spectra of the mixture $[C_2mim][CH_3CO_2]$, limonene and DEGDME.

The first step is to identify the peaks and corresponding hydrogens in the pure compounds spectra. Then, it is necessary to choose isolated peaks in the pure spectra NMR's that ate also isolated in the mixture NMR. Depending on the solvents used, these can be slightly deviated. In this case A-1 (3 H) , B-8 (2H) and C-4 (1 H) were selected. In parenthesis is

represented the number of hydrogens that correspond to each peak selected. Then it is necessary to calculate the area below each peak selected in the NMR of the mixture using peak integration.

The first peak integrated is used as a reference, by inserting the number of hydrogens it corresponds. In Figure 9 the reference was set in limonene's peak (B-8), which represents 2 hydrogens. Per last, all the peaks are automatically integrated and the software gives the final areas in proportion with the reference. Using Equation 3 it is possible to calculate the molar fraction of each component on each phase

$$x_i = \frac{\frac{a_i}{nrH_i}}{\frac{a_i}{nrH_i} + \frac{a_j}{nrHj} + \frac{a_k}{nrH_k}} \tag{3}$$

where a_i is the area of the peak and nrH_i corresponds to the number of hydrogens that which that peak represents in the molecule. In Figure 9 an example of the calculation can be found. All the calculated molar fractions were represented in ternary diagrams, where each phase represents the end of a tie-line for a given system.

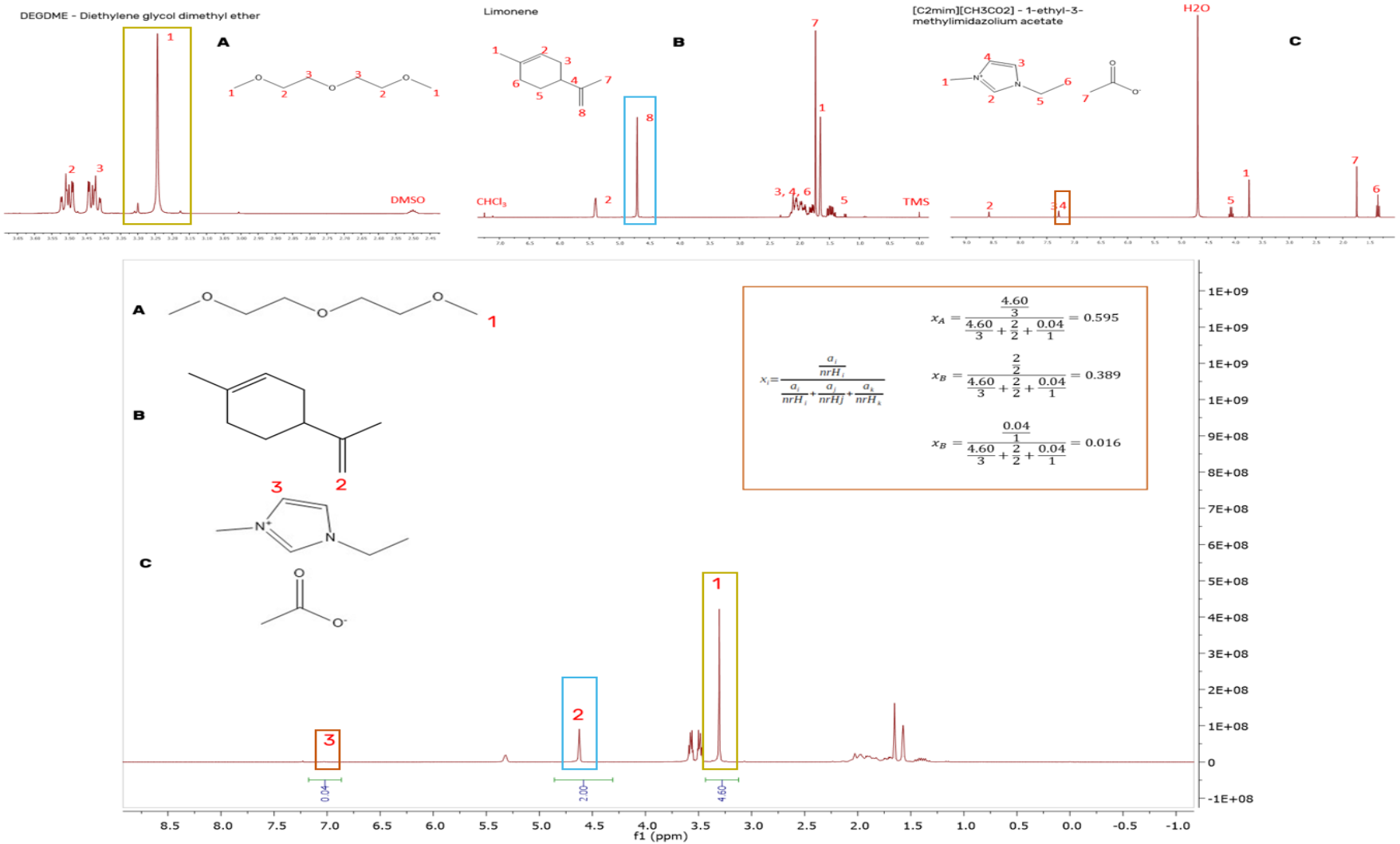


Figure 9. Example of the spectra used in the 1H NMR analysis in this work. On the top of the figure, A) (d6-DMSO, 300 MHz, [ppm]: δ 3.53-3.47 (m,2H, C(2)), 3.45-3.40 (m, 2H, C(3)), 3.25 (s, 3H, C(1)); B) 1H NMR (CDCl3, 300 MHz, [ppm]:δ 5.40 (t, 1H, C(2)), 4.70 (s, 2H, C(8)), 2.16-1.75 (m, 2H, C(3), 2H, C(6), 1H, C(4)) , 1.73 (s, 3H, C(7)), 1.65 (s, 3H, C(1)), 1.54-1.39 (m, 2H, C(5)); C) (D20, 300 MHz, [ppm]:δ 8.58 (s, 1H, C(2)), 7.36-7.33 (m, 1H, C(3)), 7.29-7.26 (m, 1H, C(4)), 4.12-4.03 (m, 2H, C(5)), 3.74 (s, 3H, C(1)), 1.74 (s, 3H, C(7)), 1.35 (t, 3H, C(6)). On the bottom part of the figure is a spectrum of one of the samples from the mixture limonene, DEGDME and [C2mim][CH3CO2].

4. Experimental Results

“A positive attitude causes a chain reaction of positive thoughts, events and outcomes. It is a catalyst and it sparks extraordinary results”- Wade Boggs

As stated before, COSMO-RS is a very interesting predictive tool and many examples of its use in many areas can be found in literature.[6,23,39] In this work, COSMO-RS was used to narrow the number of ionic liquids that could be experimentally applied in the linalool/limonene separation and to select the solvent to be used as a co-extractant. However, these predictions must be always experimentally validated and thus, the experimental LLE was measured and compared with the COSMO-RS predictions.

The experimental ternary diagrams obtained in this work and the correspondent COSMO-RS prediction are presented and discussed in detail in this section. All the data used in the following ternary diagrams can be found in Support Information.

All the mixtures were prepared considering the middle of the tie-lines predicted by COSMO-RS to obtain phases of the same size. Figure 10 display the ternary diagrams with the experimental results measured in this work in black and the COSMO-RS predictions in grey. Eight ionic liquids were used in this part of the work but only seven are represented in ternary diagrams. The samples prepared using 1-butyl-3-methylimidazolium methanesulfonate were miscible from the start, not forming two phases.

By analysing Figure 10, it is possible to observe that in the ternary phase diagrams containing limonene (**a**, **b**, **d**, **e**, **f**, **g** and **i**), the miscibility of limonene with DEGDME and the ILs is smaller than for linalool (**c** and **h**), probably due to the interactions of the hydroxyl group of linalool with the ionic liquids.

Most of the experimental tie-lines follow the trend predicted by COSMO-RS. However, the experimental tie-lines do not completely match the predicted ones, with COSMO-RS being over-predicting of the solvents separation capability for the tested mixtures. As stated by many authors[23,67], it can be concluded that COSMO-RS is a strong predictive tool, however cannot be used for quantitative analysis, i.e., COSMO-RS can be used to predict what will happen in a separation process, however cannot be relied in the numerical results given.

From all the ionic liquids studied in this work, $[C_4mim][HSO_4]$ presents the biggest immiscible region for both terpenes (Figure 10: **b** and **c**), for both experimental results and COSMO-RS predictions. These immiscible regions indicate a plausible extraction using a liquid-liquid separation unit dimensioned (equilibrium stages) aiming at obtaining two streams, one rich in DEGDME and linalool and the other rich in IL and limonene, as you can see with Figure 10 - **b** and **c**. For all the 8 immidazolium-based ILs studied, only 2 provided results to create a ternary phase diagram with linalool, $[C_4mim][CH_3SO_3]$ and $[C_4mim][HSO_4]$ due to miscible samples and problems with retrieving a sample for analysis without contamination. This appears to happen due to the solubility between linalool and $[C_2mim]$-based ILs, likely due to

the preferential interaction of its hydroxyl group with ionic liquids with bigger polarity and points to an over-prediction of COSMO-RS.

According to Arce *et al.*[24], $[C_2mim][CH_3SO_3]$ is a good extractant for the citrus essential oil deterpenation, what is in agreement with the COSMO-RS predictions performed in this work. Nevertheless this should be experimentally confirmed. Besides, when DEGDME is used as a co-extractant, the mixture becomes completely miscible not enabling the production of any tie-lines for study. The same conclusion can be applied when considering the work of Lago *et al.*[28] that studied this deterpenation process using $[C_2mim][CH_3CO_2]$ and $[C_4mim][CH_3CO_2]$. The authors stated that the best option for this separation was using $[C_4mim][CH_3CO_2]$, that is in agreement with COSMO-RS predictions. Even though these results need to be experimentally tested. Once again, the lack of immiscible samples in the experimental results for these two ionic liquids do not allow the confirmation of efficiency in the use of DEGDME as a co-extractant.

To summarize, according to the COSMO-RS predictions done in this work, the addition of DEGDME as a co-solvent to the systems studied improve the extraction for the mixtures. Overall the experimental results obtained in this work are in agreement with COSMO-RS predictions. The predicted selectivities are supported by the experimental results but mostly on those for the systems composed of $[C_2mim][CH_3CO_2]$, $[C_4mim][CH_3CO_2]$ and $[C_4mim][CH_3SO_3]$ where the addition of linalool to an immiscible IL + DEGDME mixture leads to a homogenous mixture, denoting the favourable interaction imposed by the alcohol, allowing one to expect that on a real matrix the selectivity would be much higher than that predicted. However, further experimental data (quaternary mixtures with both terpenes, the ionic liquid and the co-solvent) is required in order to evaluate and support the conclusions.

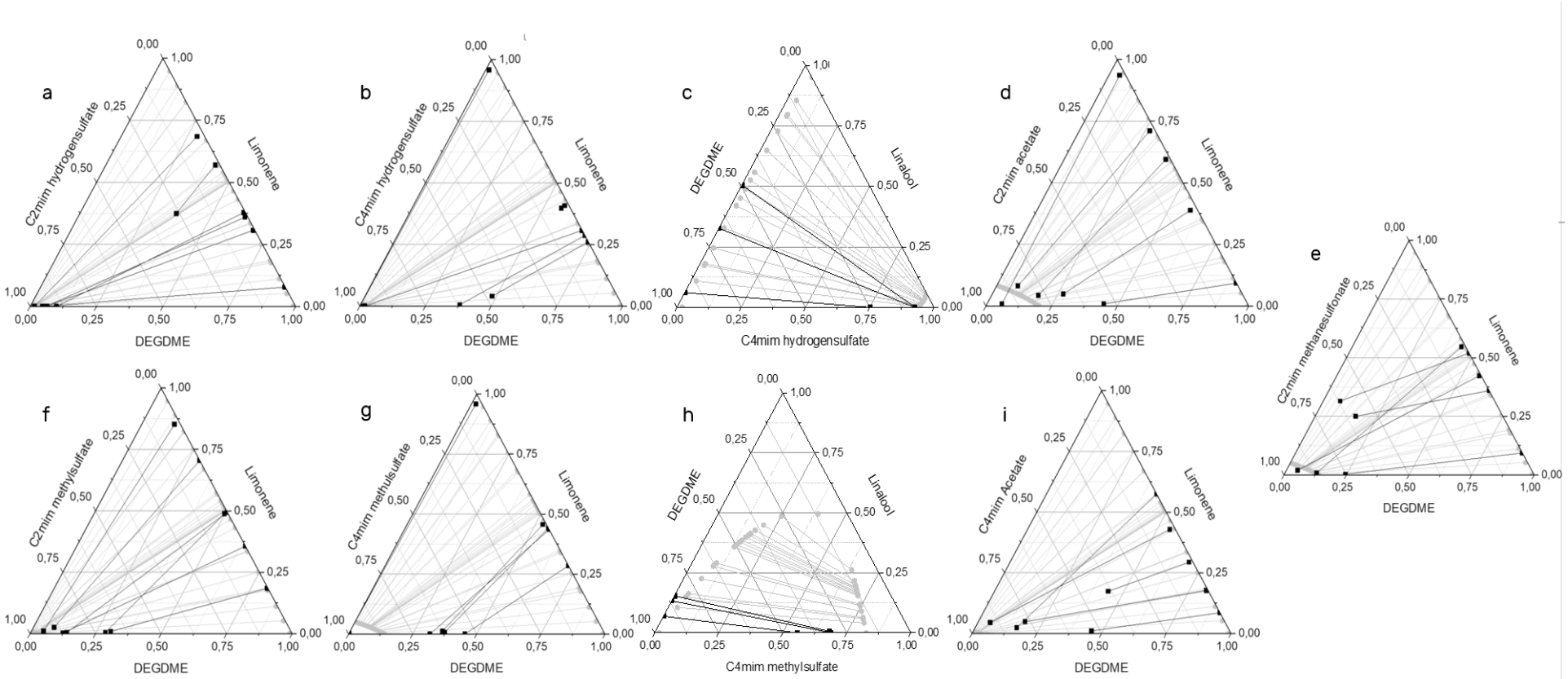


Figure 10. Experimental ternary diagrams for the studied ionic liquids, terpenes and DEGDME at 298.15 K. a) 1-ethyl-3-methylimidazolium hydrogensulfate and limonene; b) 1-butyl-3-methylimidazolium hydrogensulfate and limonene; c) 1-butyl-3-methylimidazolium hydrogensulfate and linalool; d) 1-ethyl-3-methylimidazolium acetate and limonene; e) 1-ethyl-3-methylimidazolium methanesulfonate and limonene; f) 1-ethyl-3-methylimidazolium methylsulfate and limonene; g) 1-butyl-3-methylimidazolium methylsulfate and limonene; h) 1-butyl-3methylimidazolium methylsulfate and linalool; i) 1-butyl-3-methylimidazolium acetate and limonene.

5. Conclusion

“ Reconhecer a realidade como uma forma da ilusão, e a ilusão como uma forma da realidade, é igualmente necessário e igualmente inútil. A vida contemplativa, para sequer existir, tem que considerar os acidentes objectivos como premissas dispersas de uma conclusão inatingível; mas tem ao mesmo tempo que considerar as contingências do sonho como em certo modo dignas daquela atenção a elas, pela qual nos tornamos contemplativos.” - Livro do Desassossego, Bernardo Soares

The present work reports a broad study on ionic liquids as extractants for the deterpenation of citrus essential oil. To narrow to a feasible number the possible ionic liquids to be used in this extraction, COSMO-RS, a predictive tool that allows the calculation of large number of properties using only the molecular structure of the compounds, was used. COSMO-RS was used to screen around 11,000 different ionic liquids, allowing to identify 516 with selectivities ranging from 60 to 197. Among the ILs with the highest predicted selectivity one can identify those based on ammonium and guanidinium cations, combined with carboxylate anions (with selectivities higher than 120) as the most interesting. However, not having those available, 8 other ionic liquids, based on $[CH_3CO_2]^-$, $[CH_3SO_3]^-$, $[CH_3SO_4]^-$ and $[HSO_4]^-$ anions and $[C_2mim]^+$ and $[C_4mim]^+$ cations, were evaluated experimentally.

Many have proposed ionic liquids as solvents for the intended separation, but the reported selectivities are low and thus, aiming at improving the separation capacity of the ionic liquids, to deterpenate the citrus essential oil, the use of a co-extractant was evaluated. Several solvents from three families, alkanes, glycols and glymes, known to form large immiscibility regions with the ILs, were studied. The terpene-IL-solvent, terpene-terpene-solvent and terpene-terpene-IL ternary phase diagrams were evaluated allowing to identify the diethylene glycol dimethyl ether (DEGDME) as the best co-solvent.

Several mixtures were prepared and the phases quantified by ^1H NMR analysis. The LLE results were compared against those predicted by COSMO-RS showing that the model allows a good qualitative prediction of the equilibrium, although some over-prediction, regarding the efficiency of the solvents in this extraction, is observed across all the studied systems. From all the ILs studied, it is possible to conclude that the best IL is $[C_4mim][HSO_4]$ with immiscibility regions that allow one to picture a plausible extraction. It is also possible to conclude that the addition of a co-solvent in the extraction improves the systems selectivities. However, these results should be experimentally confirmed, to allow us to proceed with a study with more complex mixtures or real matrices.

The choice of an extractant for a deterpenation cannot be done based only in experimental results, but also in economical and health indicators, such as costs and toxicity. So far, all the ionic liquids present in this work can be considered green and non-toxic, but information about the economical aspects is still needed.

The choice of the essential oil to be used as raw material for a given terpene should also be based on economical aspects, to decide between synthesis or extraction, and which method to use to extract. In the case of citrus essential oil, that has great availability in the market as well as it main constituents, might not be essential to find a new technique to

separate it. However, this work is the beginning of a concept proof that can be applied to expensive essential oils that contain expensive terpenes in its constitution.

Future investigations should be focused on LLE studies for ILs containing ammonium and guanidinium based cations since COSMO-RS predicts a great selectivity for these ILs families. Moreover, it would be important to improve the experimental setup used, namely the way how the separation of the phases is done, as extend the description of the phase diagrams. On the other hand, the investigation of the LLE data of real matrices stands also relevant for a future separation process. Furthermore, the COSMO-RS predictive capability could be enhanced by using the ionic liquids as an ion pair instead of the combination of a cation and an anion procedure that could be also evaluated.

Having selected solvents and co-solvents with high potential for the intended separation the development of a continuous separation unit, and its technical evaluation stands vital.

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